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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,058	HARDIE ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,16,19-29 and 31-35* is/are pending in the application.

4a) Of the above claim(s) *1,2,6-12,14,21-29 and 31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,16,19 and 20* is/are rejected.

7)☒ Claim(s) *3-5,16,19 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *Nov 28 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Miscellaneous Communication of April 21, 2010 herein is withdrawn.

Applicants' election, with traverse, of (1) an LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6; (2) a STRAD polypeptide comprising a C- terminal pseudokinase domain, said C-terminal pseudokinase domain comprising the C- terminal sequence Trp-Glu-Phe; (3) an M025 polypeptide comprising SEQ ID NO: 11; and (4) the substrate comprising SEQ ID NO: 110, in their response of January 27, 2010, is acknowledged. Based on prior election and prosecution as well as the election of January 27, 2010, the elected invention is directed to a composition comprising an LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a STRAD polypeptide comprising a C- terminal pseudokinase domain, said C-terminal pseudokinase domain comprising the C- terminal sequence Trp-Glu-Phe, and an M025 polypeptide comprising SEQ ID NO: 11 as well as a method, using said preparation and the substrate of SEQ ID NO: 110, for identifying modulators of LKB1.

Applicants' traversal is based on the following arguments. The reasons these arguments are not, or are, found to be persuasive are explained following each argument.

(A) No basis is provided for requiring restriction. "When making a lack of unity of invention requirement, the examiner must (1) list the different groups of claims and (2) explain why each group lacks unity with each other group (i.e., why there is no single general inventive concept) specifically describing the unique special technical feature in each group." MPEP 1893.03(d). In this case, the Examiner has done neither. The Examiner provided no explanation as to why the claims lack unity of invention; for that matter, the Examiner has not even stated that the claims lack unity of invention. Under the Patent Cooperation Treaty, the requirement for

unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. See PCT § 13.2.

(A) Reply: The action of October 27, 2009 lists the different groups and states:

> "The inventions listed as Group II relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they comprise the same or corresponding special technical feature, an in vitro composition comprising LKB 1, STRAD, and MO25 polypeptides and a method for identifying LKB 1 activity modulators using said in vitro composition. The products of Groups III, VI, XI, and XII are not so linked to Group II as to be encompassed by said single general inventive concept because said products do not share a common structure and function with the product of Group II. The methods of Groups IV, V, and VII-X are not linked so linked to Group II as to be encompassed by said single general inventive concept because said methods do not share the same modes of operation, functions, or effects of the methods of Group II. For each of Groups II, III, VI, XI, and XII, the sub-inventions thereof do not share a common structure and function. For each of Groups II, IV, V, and VII-X, the sub-inventions thereof do share the same modes of operation, functions, or effects."

Thus, Group II was considered to have Unity of Invention in that the claims of said group share the special technical feature of an in vitro composition comprising LKB 1, STRAD, and MO25 polypeptides. Groups I and III-XII, and sub-groups thereof, set forth in the action of October 27, 2009, do not comprise said special technical feature because Groups I and III-XII do not make or use an in vitro composition comprising LKB 1, STRAD, and MO25 polypeptides.

(B) Far from explaining why the claims lack unity of invention, the Office Action states that there is unity of invention among the claims. The Examiner states on page 5, first paragraph:

> "The inventions listed as Group II relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they comprise the same or corresponding special technical feature, an in vitro composition comprising LKB 1, STRAD, and M025 polypeptides and a method for identifying LKB 1 activity modulators using said in vitro composition."

As it is the Examiner's position that the inventions listed as Group II (currently elected) comprise the same or corresponding technical feature, it must follow that there is unity of

invention among the inventions listed as Group II. As there is unity of invention, restriction is improper.

(B) Reply: A requirement for election of species of a generic invention having Unity of Invention in an application filed under 35 USC 371 is proper under PCT Rule 13.1. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claims are generic, Markush claims: 3-5, 16, 19, and 20.

The instant claims recite any preparation comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure, with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15, wherein the LKB1 phosphorylates any AMPK, the STRAD binds to any complex consisting of any LKB1 and any MO25, and MO25 binds to any STRAD. Currently, the Markush groups of these claims, as amended, do not share a special technical feature because they do not make a contribution over the prior art; see the rejections under 35 USC 102 and 103, below. In addition, the substrates recited in Claim 19 do not share a common structure. In fact, the current claims of Group II do not share a special technical feature because the subject matter recited does not define a contribution over the prior art. Nonetheless, based or prior prosecution and in the interest of customer service, all claims of Group II are herein examined.

(C) Furthermore, the Office Action does not state between which inventions restriction is required. The Office Action does not define any inventions that lack unity, but merely states that Applicants are required to elect "one specific" polypeptide for each of LKB1, STRAD, MO25

and the substrate. Applicants are uncertain as to what is required. Furthermore, Applicants are uncertain as to what is required with regard the requirement that Applicants "elect one specific substrate (SEQ ID NO:) encompassed by Claims 3-5, 16, and 19-20." Claims 3-5 and 16 do not recite the limitation of a substrate. Independent Claims 3 and 19 are directed to an embodiment of STRAD that comprises a C-terminal pseudokinase domain comprising the C-terminal sequence Trp- Glu-Phe. Applicants do not understand among which plurality of inventions Applicants are required to elect regarding STRAD.

(C) Reply: Claims 3-5 and 16 encompass a preparation comprising a LKB1 protein, a STRAD protein, and a MO25 protein. Claims 19 and 20 encompass using said preparation. Therefore, Applicants were required to elect one specific LKB1 protein, one specific STRAD protein, and one specific MO25 protein for all of Claims 3-5, 16, 19, and 20. In addition, Applicants were required to elect one specific substrate, as encompassed by Claims 19 and 20.

In an application where the claim set encompasses only generic claims, or limitations are recited only generically, it is proper, based on the disclosure, to require applicants to elect a species encompassed by said generic claims or limitations (see MPEP 80.02(a)(B)).

(D) When the Office takes the position that inventions as claimed are independent or distinct under the criteria of MPEP § 806.05(c) - § 806.06, the Office must establish that there would be a serious burden if restriction is not required. The Examiner has provided no evidence or explanation whatsoever as to why, in the absence of restriction, there will be undue burden on the Office. Applicants submit that there is no undue burden in examination of the claims as currently presented.

(D) Reply: There would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

(E) The requirements for unity of invention among members of a Markush group are explained in Annex B of the Administrative Instructions Under the PCT. Elements of a Markush group share unity of invention "when the alternatives are of a similar nature." Annex B (f). The alternatives are of a similar nature if (1) all alternatives have a common property or activity, and (2)(a) all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains or (2)(b) a common structure is present. In this case, the requirements are met by all of the Markush groups in question. The LKB1 Markush group of Claim 3(a) and Claim 19(a)(ii)(A) include the elements "residues 44-343 of SEQ ID NO: 6, a variant thereof having a conservative substitution, and a variant thereof having at least 65% sequence homology." Both claims further recite that the LKB 1 polypeptide phosphorylates or activates AMPK.

(E) Reply: See (B), above.

(F) Even if one were to assume that the members of the Markush group are not few in number (Applicants do not admit this assumption), the proper action would be an election of species requirement, not a restriction requirement.

(F) Reply: Claim 3(c) comprises the Markush group of SEQ ID NO: 11-15, while Claim 19 comprises said Markush group as well as the Markush group of SEQ ID NO: 16-21, 23, 24, 29-31, 33, 35, and 110. The Examiner fails to see that specification provides evidence that all of SEQ ID NO: 11-15 binds to a STRAD protein, what region of any MO25 protein is responsible for binding to any STRAD protein, or whether said responsible region is conserved in all of SEQ ID NO: 11-15. Thus, evidence has not been provided that the polypeptides of SEQ ID NO: 11-15 share a special technical feature linked by a common structure and function. Likewise, the Examiner fails to see that specification provides evidence that all of SEQ ID NO: 16-21, 23, 24, 29-31, 33, 35, and 110 share a special technical feature linked by a common structure and function.

The restriction requirement is still deemed proper and is therefore made FINAL.

Applicants' Request for Continuing Examination of August 25, 2009 and amendment of September 23, 2009, in response to the Final Rejection of February 25, 2009, are acknowledged. The currently pending claim set was filed on January 27, 2010. It is acknowledged that Claims 3 and 19 have been amended. Claims 1-12, 14, 16, 19-29, 31-35 are pending. Claims 1, 2, 6-12, 14, 21-29, and 31-35 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 3-5, 16, 19, and 20 are hereby reexamined.

Priority

The priority date granted for the claims, as amended, is June 21, 2006, the filing date of the instant application. It is noted that none of PCT/GB04/03096, GB 0316725.1, or GB 0330078.7 discloses SEQ ID NO: 12 or 14, as disclosed by sequence listing filed January 17, 2006. In response to this action, it is requested that Applicants point out support for all recited sequences in each priority document.

Sequence Listing Objections

The sequence listing filed January 17, 2006 is objected to because SEQ ID NO: 16 and 22 are identical. Applicants are required to correct the sequence listing and the specification accordingly.

Drawings Objections

Figure 2A is objected to because the sequences therein indicated to be SEQ ID NO: 12 and 14 are not the sequences disclosed as SEQ ID NO: 12 and 14 in the sequence listing filed January 17, 2006.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

Claim 16 is objected to for "ratios are", which should be corrected to "ratio is".

Claims 3-5, 16, 19, and 20 are provisionally objected to for reciting non-elected subject matter.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 16, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Prior rejection of Claim 19, because recitation of "identifying a compound for modulating cellular LKB1 activity…a preparation according to claim 3" renders the claim indefinite, is maintained. In support of their request that said rejection be withdrawn, Applicants

provide the following arguments. Claim 19, as amended, recites the steps of contacting a substrate polypeptide with a LKB1-STRAD-MO25 complex and measuring the phosphorylation of the substrate polypeptide. Applicants submit that a person of ordinary skill in the art would have understood what is meant by the listed steps at the time of filing; therefore the claim is not indefinite. Said argument is not found to be persuasive because the recited steps fail to accomplish the goal of the method, as recited to be "identifying a compound for modulating cellular LKB1 activity".

For Claim 3, the phrase "30% by weight of an LKB 1 polypeptide, a STRAD polypeptide and a recombinant MO25 polypeptide" renders the claim indefinite. It is unclear whether said phrase means each polypeptide comprises 30% by weight of the preparation or the combination of the three polypeptides comprises 30% by weight of the preparation. The skilled artisan would not know the metes and bounds of the recited invention. Claims 4, 5, and 16, as dependent from Claim 3, are indefinite for the same reason. For purposes of examination, it is assumed that "30% by weight of an LKB 1 polypeptide, a STRAD polypeptide and a recombinant MO25 polypeptide" means the preparation comprises "30% by weight of a combination an LKB 1 polypeptide, a STRAD polypeptide and a recombinant MO25 polypeptide".

For Claim 3(a)&(c), penultimate line each, the "and" is improper Markush language.

For Claim 3(a)&(c) and Claim 19(a)(i)(ii)(A)&(B), the phrase "conservative substitution" render the claims indefinite. The description on page 16 is only exemplary and does not define the metes and bounds of said phrase. Although very common in the art, the term "conservative substitution" is vague and indefinite. For example, is a Gln/Glu substitution or an Asp/Asn substitution conservative? Are Ser/Tyr and Phe/Tyr conservative substitutions? Another

situation that is indefinite is the classification of Gly and Ala; are these small polar residues, similar to Ser, Thr, Gln and Asn, or hydrophobic? Is His basic or hydrophobic? Are linear hydrophobic amino acids similar to aromatic hydrophobic amino acids? Is Cys a small polar amino acid or its own category? Is Tyr a polar amino acid or an aromatic amino acid? Lack of consensus on the answers to these questions causes the term "conservative substitution" to be indefinite.

For Claim 3(b) and Claim 19(ii)(B) the phrase "STRAD polypeptide binds to LKB1 and MO25" renders the claims indefinite. It is unclear whether said phrase means "STRAD polypeptide binds to both LKB1 and MO25" or "STRAD polypeptide binds to a complex consisting of LKB1 and MO25". The skilled artisan would not know the metes and bounds of the recited invention. Claims 4, 5, 16, and 20, as dependent from Claim 3 or 19, are indefinite for the same reason. For purposes of examination, it is assumed that "STRAD polypeptide binds to LKB1 and MO25" means "STRAD polypeptide binds to a complex consisting of LKB1 and MO25".

For Claim 3(c), the phrase "a variant of any of the foregoing having at least 65% sequence homology" renders the claim indefinite. It is unclear whether said phrase means encompasses (i) only variants having at least 65% identity to SEQ ID NO: 11-15 or (ii) variants having at least 65% identity to SEQ ID NO: 11-15 *and* variants having at least 65% identity to variants of SEQ ID NO: 11-15 having a conservative substitution. The skilled artisan would not know the metes and bounds of the recited invention. Claims 4, 5, and 16, as dependent from Claim 3, are indefinite for the same reason. For purposes of examination, it is assumed that "a

variant of any of the foregoing having at least 65% sequence homology" renders the claim indefinite encompasses only variants having at least 65% identity to SEQ ID NO: 11-15.

For Claim 19(ii)(A), penultimate line, the "and" is improper Markush language.

Claims 3, 19, and 20 are rendered indefinite for improper antecedent usage as follows.

For Claim 3(b) and Claim 19(C), "the C-terminal sequence Trp-Glu-Phe" lacks antecedent basis. Claims 4, 5, 16, and 20, as dependent from Claim 3 or 19, are indefinite for the same reason.

Any subsequent rejection, based on clarification of the above phrases and terms, will not be considered a new ground for rejection.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 3-5, 16, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph/enablement. The specification is enabling for preparations, isolated from human HEK-293 cells and Rat-2 cells, comprising endogenous LKB1, STRAD, and MO25 polypeptides. In addition, as disclosed by the specification, the prior art provides enablement for an affinity purified complex comprising a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD protein with a C-terminal Trp-Glu-Phe tail, and the recombinant human MO25 of SEQ ID NO: 11 (Boudeau et al, 2003). However, the specification does not reasonably provide enablement for a preparation comprising any LKB1 protein comprising a

sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure, with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 3-5 and 16 are so broad as to encompass any preparation comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15, wherein the LKB1 phosphorylates any AMPK, the STRAD binds to any complex consisting of any LKB1 and any MO25, and MO25 binds to any STRAD. Claims 19 and 20 are so broad as to encompass any method for identifying a LKB1 modulator using said preparation and any

substrate comprising a sequence with at least 65% identity to any one of SEQ ID NO: 16-21, SEQ ID NO: 23-35, or SEQ ID NO: 110. It is noted that by use of "comprising" language, these claims encompass polypeptides, wherein the activity is not derived from the sequence homologous to SEQ ID NO: 6, 11-15, 16-21, 23-35, and 110.

The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of preparations and methods broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to preparations isolated from human HEK-293 cells and Rat-2 cells and reference to the prior art, which provides enablement for an affinity purified complex comprising a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD protein with a C-terminal Trp-Glu-Phe tail, and the recombinant human MO25 of SEQ ID NO: 11 (Boudeau et al, 2003).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993;

Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 3-5 and 16, which encompasses all preparations comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15, wherein the LKB1 phosphorylates any AMPK, the STRAD binds to any complex consisting of any LKB1 and any MO25, and MO25 binds to any STRAD. The specification does not support the broad scope of Claims 19 and 20, which encompasses all methods for identifying a LKB1 modulator using said preparation and any substrate comprising a sequence with at least 65% identity to any one of SEQ ID NO: 16-21, SEQ ID NO: 23-35, or SEQ ID NO: 110. The specification does not support the broad scope of Claims 3-5, 16, 19, and 20 because the specification does not establish: (A) regions of each recited protein's structure which may, or may not, be modified without affecting the desired activity; (B) the general tolerance of the desired activities to modification of the recited proteins and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including any number of preparations comprising proteins with an enormous number of amino acid modifications of the proteins of SEQ ID NO: 11-5, SEQ ID NO: 16-21, SEQ ID NO: 23-35, and SEQ ID NO: 110. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of proteins having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants did not make any specific arguments in their remarks of September 23, 2009 that bear on the above rejection.

Written Description

Claims 3-5 and 16 are rejected under 35 U.S.C. 112, first paragraph/written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of preparations comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein having any structure, with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15. The specification teaches only two such preparations, from human HEK-293 and rat-2 cells, while the prior art teaches the structure of only a single representative species of such preparations. Moreover, the specification fails to describe any other representative species by any identifying structural characteristics or properties other than the functionality of

encompassing a LKB1, STRAD, and MO25 protein, wherein the LKB1 phosphorylates any AMPK, the STRAD binds to any complex consisting of any LKB1 and any MO25, and MO25 binds to any STRAD. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 19 and 20 are directed to a genus of methods for identifying LKB1 modulators using any preparations comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15 and any substrate having at least 65% identity to any one of SEQ ID NO: 16-21, SEQ ID NO: 23-35, or SEQ ID NO: 110. The specification teaches only a two representative species of such methods, using preparations from human HEK-293 and rat-2 cells and the substrate LSNMMSDGEFLRTSCGSPNRRR (SEQ ID NO: 110). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for identifying LKB1 modulators. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the

claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In support of their request that the prior rejection under 35 U.S.C. 112, first paragraph/written description, be withdrawn, Applicants provide the following argument, which is relevant to the rejections above. The claims now recite particular structures and functions of LKB1, STRAD, and MO25, so that they no longer encompass "any structure." This argument is not found to be persuasive for the following reasons. As explained above, Claims 3-5, 16, 19, and 20 are so broad as to encompass any preparation comprising any LKB1 protein comprising a sequence with at least 65% identity to 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% identity to any one of SEQ ID NO: 11-15, wherein the LKB1 phosphorylates any AMPK, the STRAD binds to any complex consisting of any LKB1 and any MO25, and MO25 binds to any STRAD. Claims 19 and 20 encompass using any said preparation. The two examples in the specification and the one example in the prior art fail to described features and attributes of the full scope of the recited genus of preparations and methods such that the skilled artisan would recognize that Applicants were in possession at the time of filing.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This claim is directed to a genus of preparations comprising LKB1, STRAD, and MO25 proteins in a ratio of 1:1:1. The specification teaches no representative examples of such preparations. Moreover, the prior art teaches that MO25 binds to more than one site on the

LKB1/STRAD complex (Boudeau et al; pg 5112, parg 1). Given this lack of description of representative preparations encompassed by the genus of the claim, and the teachings of the prior art, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

For these reasons and those explained in the prior action, rejection of Claims 3-5, 16, 19, and 20 under 35 U.S.C. 112, first paragraph/written description, is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 3 is rejected under 35 U.S.C. 102(b), as being anticipated by Tang et al, 2000 (US6071721). Tang et al teaches a human MO25 protein, (hCBP/SEQ ID NO: 1 therein) having 81% identity with SEQ ID NO: 11 herein (see enclosed alignment). Tang et al further teaches a preparation that comprises a recombinant form of said human MO25 protein isolated from human host cells (col 18, parg 3). Said human-derived preparation would inherently comprise (i) a human LKB1 protein having at least 65% homology to residues 44-343 of SEQ ID NO: 6 and

(ii) a human STRAD protein that binds to the LKB1 protein and the human MO25 protein and comprises a C-terminal Trp-Glu-Phe tail. Therefore, Claim 3 is rejected under 35 U.S.C. 102(b), as being anticipated by Tang et al, 2000.

Claim 3 is rejected under 35 U.S.C. 102(b), as being anticipated by Den Daas et al, 2000 (WO200078947). Den Daas et al teaches the human MO25 protein of SEQ ID NO: 11 herein (AAB48970; see enclosed alignment). Den Daas et al further teaches a preparation that comprises a recombinant form of said human MO25 protein isolated from human host cells using an antibody (pg 12, parg 3; pg 17, parg 4). Said human-derived preparation would inherently comprise (i) a human LKB1 protein having at least 65% homology to residues 44-343 of SEQ ID NO: 6 and (ii) a human STRAD protein that binds to the LKB1 protein and the human MO25 protein and comprises a C-terminal Trp-Glu-Phe tail. Therefore, Claim 3 is rejected under 35 U.S.C. 102(b), as being anticipated by Den Daas et al, 2000.

Claims 3-5 are rejected under 35 U.S.C. 102(b), as being anticipated by Boudeau et al, October 2003 (IDS). Boudeau et al teaches that an affinity purified complex comprising the recombinant human MO25 of SEQ ID NO: 11 also comprises a recombinant human STRAD protein with a C-terminal Trp-Glu-Phe tail and a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6 (Figs 6&7). Therefore, Claims 3-5 are rejected under 35 U.S.C. 102(b), as being anticipated by Boudeau et al, 2003.

Claims 3-5, 16, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardie et al, 2005. Hardie et al teaches preparation, 30% by weight and 1:1:1 ratio, of the recombinant human LKB1 polypeptide of residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD having a C-terminal Trp-Glu-Phe, and the recombinant human MO25 protein of

SEQ ID NO: 11 (Fig 7; Claims 15-17). Hardie et al further teaches use of said preparation to identify LKB1 modulators (Claims 20-26 and 35). Therefore, Claims 3-5, 16, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardie et al, 2005.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boudeau et al, 2003 in view of Mohamed et al, 2001. Teachings of Boudeau et al are described above. Boudeau et al further teaches a method for measuring phosphorylation of myelin basic protein by their LKB1-comprising complex (Fig 9). Boudeau et al does not teach using said method to identify modulators of LKB1. However, identifying modulators of affinity purified kinases was well known in the art. For example, Mohamed et al teaches identifying an in vitro inhibitor of MuSK phosphorylation by purified Src-class kinases (Fig 6). It would have been obvious to a person of ordinary skill in the art to adapt the method of Boudeau et al to screen for modulators of LKB1. Motivation to do so is provide by the desire to identify modulators of LKB1. The expectation of success is high, as all methods are standard in the art. Therefore, Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boudeau et al, 2003 in view of Mohamed et al, 2001.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Boudeau et al, 2003 and Mohamed et al, 2001 in view of Hong et al, 2003. The combination

of Boudeau et al and Mohamed et al is described above. Said combination does not teach using AMPK as a substrate in the method to identify modulators of LKB1. Hong et al teaches that AMPK is a substrate of LKB1 (Fig 4). It would have been obvious to a person of ordinary skill in the art to adapt the method rendered obvious by the combination of Boudeau et al and Mohamed et al to screen for modulators of LKB1 using AMPK as a substrate. Motivation to do so is provide by the advantage of using a more biologically relevant substrate. The expectation of success is high, as all methods are standard in the art. Therefore, Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Boudeau et al, 2003 and Mohamed et al, 2001 in view of Hong et al, 2003.

Allowable Subject Matter

No claims are allowable

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Nonetheless, in the interest of public service this action is non-final.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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